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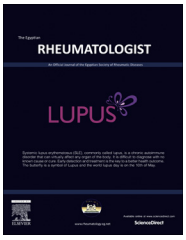

ORIGINAL ARTICLE

Assessment of premature coronary atherosclerosis in patients with systemic lupus erythematosus disease

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KEYWORDS

Systemic lupus erythematosus;
Coronary atherosclerosis;
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Abstract *Introduction:* Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that affects mainly young women. The incidence of myocardial infarction is 5 times higher in SLE patients than in the general population.

Aim of the work: The aim of our study was to assess the frequency and extent of coronary artery calcification as measured by multidetector computed tomography (CT) in SLE patients and to identify the associated variables.

Patients and methods: Thirty SLE patients and 30 matched healthy controls were included in the study. Patients were not known to have atherosclerosis. Patients and controls were subjected to full history taking, clinical examination, laboratory investigations including complete blood count, urine analysis, serum urea, creatinine, homocysteine, triglycerides, total cholesterol, high and low density lipoproteins. Multi detector CT study of the coronaries was performed.

Results: Coronary calcification was detected in 4 (13.3%) of the patients and none of the control. The homocysteine level was significantly higher in the patients (13.42 ± 5.33 μmol/L) compared to the control (9.39 ± 1.48 μmol/L) ($p = 0.002$). The calcium score was 42 ± 111.09 in the patients and zero in the control. The calcification score of the 4 patients was between 101 and 400. Patients with calcification had significantly higher cholesterol, triglycerides and homocysteine levels ($p < 0.0001$, $p = 0.032$ and $p = 0.002$, respectively). The calcium score significantly correlated with the serum cholesterol ($r = 0.54$, $p = 0.002$) and homocysteine level ($r = 0.78$, $p = 0.001$).

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Conclusion: Premature coronary artery calcification is more common in SLE patients than in the general population. Subclinical atherosclerosis in SLE is associated with traditional risk factors like hypercholesterolemia and hypertriglyceridemia as well as increased homocysteine level.

1. Introduction

SLE is an autoimmune disorder characterized by multisystem microvascular inflammation with the generation of autoantibodies. Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease, including genetic, racial, hormonal, and environmental factors [1,2]. Several key player factors play a significant role in the pathogenesis of SLE such as cytokine overproduction [3,4], oxidative stress [5] and apoptosis [6]. Comorbidities as metabolic syndrome [7], dyslipidemia and atherosclerosis [8] could lead to functional disability, impaired quality of life and significantly affect the disease activity and damage.

The increase in the development of atherosclerosis has been reported in different rheumatic diseases as rheumatoid arthritis [9], osteoarthritis [10], Behçets disease [11], systemic sclerosis [12] and SLE [7,13,14] among Egyptian patients. Coronary vessels of SLE patients have the usual atherosclerotic plaque. Not all cardiovascular events are due to large obstructive plaques. Smaller ones susceptible to rupture can cause occlusive events too. Acute coronary syndromes are caused by acute disruption of unstable atheroma and SLE patients are more likely to have vulnerable plaque rupture [13].

Coronary calcification is strongly associated with the prognosis. Indeed, the extent of coronary atherosclerosis (total calcium score) is the most powerful predictor of subsequent or recurrent cardiac events. This was true in the early days when calcium was detected with fluoroscopy and conventional CT. When electron beam CT calcium scores became available, the prognostic value of coronary calcification was again affirmed. The higher the calcium score, the worse the prognosis [15,16].

A systematic review which included 28 studies found that the risk of cardiovascular disease (CVD) (which included myocardial infarction, cerebrovascular disease, and peripheral vascular disease) among SLE patients at least doubled when compared with the general population. Traditional CVD risk factors, along with disease duration and activity, appear to further increase the risk. Younger SLE patients were found to have a greatest relative risk of a CVD compared with their healthy counterparts, but the absolute risk was higher in older patients [17].

The aim of our study was to assess the frequency and extent of coronary artery calcification as measured by multidetector computed tomography (CT) in SLE patients and to identify the associated variables.

2. Patients and methods

This study was carried out to evaluate premature coronary atherosclerosis in patients with SLE and measure the calcification within the coronary vessels by using Electron Beam CT Scan. Thirty patients fulfilling the Systemic Lupus International Collaborating Clinics classification criteria for SLE [18] and 30 (age and sex matched) normal control subjects were recruited for this study. Patients were recruited from internal medicine and rheumatology outpatient clinic. The study was approved by the local university ethics committee and the study performed in accordance with the ethical standards of the 1964 Helsinki declaration. All patients gave their informed consent prior to their inclusion in the study.

All the patients and control subjects were subjected to full history taking, clinical examination and ECG. Blood pressure was determined as the average of two measurements obtained 5 min apart after subjects had rested quietly in the supine position for 10 min. Subjects were considered to have hypertension if they were taking anti hypertensive agents or if they had a systolic blood pressure (SBP) of at least 140 mmHg or a diastolic BP of at least 90 mmHg. Laboratory investigations performed included complete blood count (CBC), urine analysis, serum urea, creatinine, triglycerides, total cholesterol, high and low density lipoproteins. The serum homocysteine level was assessed. Multidetector CT study of the coronaries was performed. All SLE patients received different doses of Prednisone ranging from 5 to 15 mg per day. All SLE patients were not diabetic. Patients and control subjects with history of CVD (previous stroke, myocardial infarction, angina or ischemic changes in ECG) were excluded.

2.1. Imaging procedures

All subjects underwent imaging with an Imatron C-150 scanner (Imatron). Imaging was performed with a 100-ms scanning time and a single-slice thickness of 3 mm. A total of 40 slices were obtained during single breath-holding periods. Tomographic imaging was electrocardiographically triggered at 60% of the interval between R waves. All areas of calcification within the borders of a coronary artery with a minimal attenuation of 130 Hounsfield units were computed. Subjects were included in this study only if complete data were available from their scans, without misregistration of slices owing to artifacts of motion, respiration, or asynchronous electrocardiographic triggering. A calcified coronary plaque was considered present if at least three consecutive pixels were measured (voxel size, 1.0^3 mm^3). The acquired images were reviewed at the core electron-beam CT laboratory on a NetraMD workstation (ScImage).

2.2. Calculation of calcium scores

The degree of coronary artery calcification was calculated by Agatston et al., [19]. Calcium score of zero represents the absence of detectable calcium, whereas a score of 1–100 indicates mild degree of calcification, score of 101–400 indicates

moderate degree of calcification, score greater than 400 indicates the presence of extensive coronary artery calcification. The sum of the scores for all arterial lesions provides an overall score for each subject. The correlation between this score and other variables, such as coronary risk factors was determined.

Statistical analysis: The data were coded and entered using the statistical package SPSS version 15. The data were summarized using descriptive statistics: mean, standard deviation, minimal and maximum values for quantitative variables and number and percentage for qualitative values. Statistical differences between groups were tested using Chi Square test for qualitative variables, independent sample *t* test for quantitative normally distributed variables while Nonparametric Mann Whitney test was used for quantitative variables which are not normally distributed. Correlations were done to test for linear relations between variables.

3. Results

The study included 30 SLE patients and 30 age and sex matched controls. Table 1 shows demographic and laboratory data of patients and control groups. All the values were comparable between the patients and control except for the serum homocysteine level and calcium score which were significantly higher in the SLE patients ($p = 0.002$ and $p = 0.04$, respectively). The electrocardiogram (ECG) was normal in all the patients and controls.

In the SLE patients, coronary artery calcification detected by multidetector CT was found in 4 patients (13.3%) and they had calcification scores between 101 and 400. No calcification was detected in the controls.

Table 2 shows the correlation of calcium score with the lipid profile and homocysteine in SLE patients. A comparison of clinical and laboratory data between SLE patients with and without calcification is shown in Table 3.

Table 1 Demographic and laboratory data of systemic lupus erythematosus patients and controls.

Variable Mean ± SD	SLE patients ($n = 30$)	Controls ($n = 30$)
Age (years)	32.1 ± 5.1	32.3 ± 5.4
Female:Male	19:11	19:11
Smokers *n* (%)	7 (23.3)	8 (26.7)
SBP (mmHg)	131.6 ± 21.98	125.8 ± 18.3
DBP (mmHg)	82.8 ± 13.4	82.3 ± 10.4
Hemoglobin (g/dl)	10.1 ± 1.4	12.1 ± 1.2
TLC ($\times 10^3/mm^3$)	5.6 ± 1.4	6.4 ± 1.01
Platelets ($\times 10^3/mm^3$)	250.1 ± 78.3	229.1 ± 51.04
Creatinine (mg/dl)	0.8 ± 0.3	0.8 ± 0.2
Urea (mg/dl)	40.4 ± 17.9	25.9 ± 3.1
Cholesterol (mg/dl)	200.5 ± 56.5	178.9 ± 48.9
HDL (mg/dl)	53.2 ± 8.99	50.7 ± 14.5
LDL (mg/dl)	105.8 ± 29.7	94.97 ± 24.54
Triglycerides (mg/dl)	177.97 ± 97.7	136.1 ± 36.6
Homocysteine (μmol/L)	13.4 ± 5.3	9.4 ± 1.5
Calcium score	42 ± 111.1	Zero

TLC: total leucocytic count; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein; LDL: low density lipoprotein.

Table 2 Correlation of calcium score with lipid profile and homocysteine in SLE patients.

Variable	*r*	*p*
Cholesterol (mg/dl)	0.54	**0.002**
HDL (mg/dl)	−0.02	0.9
LDL (mg/dl)	0.36	0.054
Triglycerides (mg/dl)	0.29	0.13
Homocysteine (μmol/L)	0.78	**0.001**

HDL: high density lipoprotein; LDL: low density lipoprotein. Bold values are significant at $p < 0.05$.

Table 3 Comparison of data between SLE patients with and without calcification.

Variable	Systemic lupus erythematosus patients ($n = 30$)		
Mean ± SD	With calcification	Without calcification	*p*
Age (years)	36.5 ± 5.8	31.4 ± 4.8	0.06
SBP (mmHg)	127.5 ± 22.2	132.3 ± 22.3	0.7
DBP (mmHg)	82.5 ± 12.6	82.9 ± 13.7	0.96
Cholesterol (mg/dl)	278.3 ± 7.1	188.5 ± 50.8	< **0.0001**
HDL (mg/dl)	51.3 ± 13	53.5 ± 8.5	0.65
LDL (mg/dl)	131.8 ± 28.2	101.8 ± 28.3	0.06
Triglycerides (mg/dl)	252.3 ± 47.9	166.5 ± 98.8	**0.03**
Creatinine (mg/dl)	1.1 ± 0.2	0.8 ± 0.28	0.14
Urea (mg/dl)	48.5 ± 13.7	39.2 ± 18.4	0.18
Homocysteine (μmol/L)	23.8 ± 2.2	11.8 ± 3.6	**0.002**

SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein; LDL: low density lipoprotein. Bold values are significant at $p < 0.05$.

4. Discussion

SLE is a chronic inflammatory autoimmune disease that affects mainly young women, a group usually free of atherosclerosis. The incidence of myocardial infarction is five times as high in patients with lupus as in the general population [20]. Coronary artery atherosclerosis can be detected non-invasively with the use of electron beam computed tomography (CT). The extent of coronary artery calcification in CT correlates with findings on coronary angiography and with the extent of atherosclerosis in pathological specimens and is predictive of future cardiac events [21].

In our study, we found that the coronary calcification was detected by multidetector CT in 4 (13.3%) SLE patients but no calcification was detected in control subjects. None of the 4 patients had calcium score greater than 400, the calcium score ranged 101–400 indicating a moderate degree of calcification, while in another study [22], the frequency of coronary calcification was higher, it was detected in 31% of SLE patients and 9% of the control, and the degree of calcification was higher; 15% had calcium score greater than 400. These differences in frequency and degree of calcification may be due to different factors as race, diet, genetic and environmental factors. Our results were in contrast to Kakuta et al. [23] who

found that coronary artery calcification was similar in patients and control groups.

In the present study, there was a tendency to a higher degree of calcification in patients with older age. This was similarly reported in other studies [24–26]. We also found that the level of cholesterol (200.5 ± 56.5 mg/dl) in SLE patients was higher than in the control (178.9 ± 48.9) but with no statistical significance. However, the cholesterol level was significantly higher in SLE patients with calcification (278.3 ± 7.1 mg/dl) compared to those without (188.5 ± 50.8 mg/dl) ($p < 0.0001$). The cholesterol level also significantly correlated with calcium score ($p = 0.002$). It has been found that in SLE patients with persistent hypercholesterolemia followed up for a mean of 12 years, 24% developed a new CVD event compared with only 3% of those with normal cholesterol levels [20,24].

We also found that the level of triglycerides (177.97 ± 97.7 mg/dl) in patients with SLE was higher than in control (136.1 ± 36.6 mg/dl). The level was higher in patients with calcification (252.3 ± 47.9 mg/dl) than in those without (166.5 ± 98.8 mg/dl) ($p = 0.03$).

Regarding homocysteine, its level in SLE patients (13.4 ± 5.33 μmol/L) was higher than control (9.4 ± 1.5 μmol/L) ($p = 0.002$). Homocysteine significantly correlated with calcium score ($p = 0.001$). This is similar to the results of Von Feldt et al. and Asanuma et al. who found that in SLE patients the level of homocysteine was higher than control and the coronary artery calcification (detected by electron beam computed tomography) was associated with a higher homocysteine concentration [22,27]. The disease activity and damage score were not included in this study and both may be well thought-out in further prospective researches.

In the current study, hypertension did not correlate with the calcium score in SLE patients; this finding is not similar to the study of Kiani et al., who found that the hypertension was correlated with coronary calcium [25].

In conclusion, premature coronary artery calcification is more common in SLE patients than in the general population. Subclinical atherosclerosis in SLE is associated with traditional risk factors like hypercholesterolemia and hypertriglyceridemia as well as increased homocysteine level.

Conflict of interest

None declared.

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